Short QT syndrome

Carla Giustetto,¹ Chiara Scrocco,¹
Daniela Giachino,² Charles Antzelevitch,³
Fiorenzo Gaita¹

¹Division of Cardiology, University of Turin, San Giovanni Battista Hospital, Turin, Italy; ²Medical Genetics Unit, University of Turin, San Luigi Hospital, Orbassano (TO), Italy; ³Masonic Medical Research Laboratory, Utica, New York, USA

Abstract

The short QT syndrome (SQTs) is a recently described genetic arrhythmogenic disorder, characterized by abnormally short QT intervals on surface electrocardiogram (ECG) and a high incidence of sudden death (SD) during life, including the first months of life. The inheritance of SQTs is autosomal dominant, with genetic heterogeneity. Gain-of-function mutations in 3 genes encoding potassium channels have been associated to the disease: *KCNH2* encoding I_{Kr} (SQT1), *KCNQ1* encoding I_{Ks} (SQT2), and *KCNJ2* encoding I_{K1} (SQT3). Loss-of-function mutations in 3 genes encoding the cardiac L-type calcium channel, *CACNA1C*, *CACNB2b* and *CACNA2D1* may underlie a mixed phenotype of Brugada pattern ECG (or non-specific repolarization changes in case of *CACNA2D1*) and shorter than normal QT intervals. Clinical presentation is often severe, as cardiac arrest represents the first clinical presentation in most subjects. Moreover, often a noticeable family history of cardiac SD is present. Atrial fibrillation may be observed, also in young individuals. At electrophysiological study, short atrial and ventricular refractory periods are found, and atrial and ventricular fibrillation are easily induced by programmed electrical stimulation. The outcome of patients with SQTs becomes relatively safe when they are identified and treated. Currently, the suggested therapeutic strategy is an implantable cardioverter-defibrillator (ICD) in patients with personal history of aborted SD or syncope. In asymptomatic adult patients from highly symptomatic families and in newborn children pharmacological treatment with hydroquinidine, which has been shown to prolong the QT interval and reduce the inducibility of ventricular arrhythmias, may be proposed.

Introduction

The short QT syndrome (SQTs) is a rare congenital ion channel disease characterized by an abnormally short QT interval on the surface electrocardiogram (ECG) and an increased susceptibility to life-threatening arrhythmias, in the absence of structural heart disease. The familial nature and the severe arrhythmic potential of the disease was highlighted by Gaita *et al.*¹ with the description of two unrelated families in which QT intervals between 210 and 280 ms (with QTc always < 300 ms) were associated with palpitations, syncope and sudden cardiac death across several generations. SQTs was recognized as an inherited condition and an autosomal dominant inheritance was suggested. The first report of an idiopathic constantly short QT interval dates back to 2000, when Gussak *et al.*² described one family (a 17-year-old girl with several episodes of paroxysmal atrial fibrillation (AF), her brother and their mother) who showed QT and QTc intervals < 300 ms, and an unrelated 37-year-old patient with similar ECG changes, who died suddenly before further investigations could be performed. Between 2004 and 2005 the genetic bases of the disease have been clarified with the discovery of gain-of-function mutations in three genes – *KCNH2*,³ *KCNQ1*⁴ and *KCNJ2*⁵ – that encode different potassium channels located on the cell membrane of the cardiomyocytes. More recently loss-of-function mutations in three genes coding for different subunits of the L type calcium channel – *CACNA1C*, *CACNB2b* and *CACNA2D1* – have been identified, which may be responsible for mixed phenotypes of Brugada pattern or non-specific ST changes and a shorter than normal QT interval.

Electrocardiogram

The diagnosis of SQTs is based on the detection of a constantly short QT interval at ECG. There are three points that must be considered: first, the practical difficulties in measuring the QT interval.⁶ It should be evaluated in several ECG and in multiple leads; SQTs patients typically present T waves of high voltage, so it seems reasonable to choose the lead with the highest T wave (most often V2 or V3). Second, it is difficult to define the normal QT interval because the correcting equations have several limitations. The best known correction model for QT interval is the Bazett's square root formula⁷ which is commonly used in clinical settings, although it has the limitation of over-correcting the QT interval at faster heart rates and under-correcting it at slower heart rates. Since the QT interval in SQTs patients

Correspondence: Carla Giustetto, Division of Cardiology, University of Turin, San Giovanni Battista Hospital, C.so Bramante, 88 - 10126 Torino, Italy.
Tel. +39.011.633.5571.
E-mail: carla.giustetto@unito.it

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approaches the normal values at high rates, it is advisable that it should be measured as close as possible to 60 beats/min. Despite alternative formulas have been developed (Fridericia's formula, Framingham's formula) it has become apparent that a universal correction model may not be feasible. In the early '90s, Rautaharju *et al.*⁸ investigated the ECGs of 14,379 healthy individuals and established a formula by which the expected QT interval can be calculated for a specific heart rate: QT predicted (QTp) = 65,600/(100 + heart rate).

Last point, it is still controversial which is the highest value of the QTp/QTc interval compatible with the diagnosis of SQTs. The first patients with short QT syndrome described by our group showed QTc intervals that did not exceed the 300 ms and a QT/QTp maximum of 71%.¹ With the increase in the number of observations, values of QT up to 320 ms and QTc up to 340 ms were subsequently reported.⁹ The QTc in the patients with a mixed phenotype (Brugada syndrome and short QT) and in their affected family members ranged from 330 ms to 360 ms in males and 370 ms in females (QT/QTp < 88%).¹⁰ Large population studies found that the values of QT and QTc intervals have a Gaussian distribution in the population.^{11,12} Based on this distribution, the *normal* QTc interval may be defined as a value that falls within 2 standard deviations from the mean. Consequently, the 95% of values are *normal*, while values below the 2.5 percentile and over the 97.5 percentile are respectively

too short and too long. For this reason, QTc of 360 ms or less or QT of 88% or less of the QTp have been proposed as the lower limit of the normal QTc and QT, because these correspond to the mean values minus 2 standard deviations in the general population.

However, a short QT interval in itself is not always predictive of an adverse prognosis; in fact in the above-mentioned studies no sudden death was associated with a QT interval shorter than normal. Due to the overlapping range of QT intervals in affected individuals and general population one must not rely only on the detection of a short QT on ECG to make a diagnosis of SQTs.

Concerning the ECG characteristics, SQTs¹ is characterized by tall, peaked and symmetrical T waves, preceded by a short or absent ST segment. Furthermore, often the Tpeak-Tend ratio is increased.¹³ In the SQTs2⁴ and in most of non-genotyped subjects, the T wave is still tall and symmetrical, despite being less sharp (Figure 1). In SQTs3⁵ the T wave appears peaked and asymmetrical, with a quite normal ascending component and a rapid descending phase. In cases of the mixed phenotype, short QT intervals alternate with a Brugada-type ST elevation in right precordial leads at baseline or after administration of ajmaline.

In a work by Watanabe *et al.*¹⁴ it is reported that 24 of 37 (65%) patients with SQTs displayed early repolarization at ECG, characterized by J-point elevation in the infero-lateral leads, suggesting also an association with arrhythmic events. Twenty-five of them were previously reported in literature and 12 referred to their institution. In the EuroShort Registry (unpublished data from our centre) however, this percentage is much lower (33%).

Genetics and molecular basis

Shortly after its description, several mutations in three different genes encoding cardiac potassium channels have been associated to SQTs (Table 1).

The genetic screening in the first reported families with SQTs and sudden cardiac death led to the identification of 2 different missense mutations resulting in the same amino acid change (from a polar uncharged asparagine at codon 588 to a positive charged lysine: N588K) in the S5-P region of the cardiac I_{Kr} channel *KCNH2* (HERG). Functional studies revealed that the mutations increase I_{Kr} function, leading to a shortening of the action potential duration and reducing the affinity of the channels to the traditional I_{Kr} blockers, such as sotalol.³ This genetic variant has been defined short QT syndrome type 1 (SQT1). It is interesting to note that mutations determining a

reduced function of I_{Kr} are responsible for long QT syndrome (LQTS) type 2. The same N588K mutation in *KCNH2* was later found in a third family exhibiting only AF.¹⁵

Recently, a new mutation in the *KCNH2* gene has been discovered. Sun *et al.*¹⁶ identified a missense mutation resulting in the amino acid change T618I (threonine to isoleucine at position 618) in four members of a Chinese family with a strong history of SD. This residue is located in the pore helix region of HERG channel. *In vitro* analyses showed that this mutation leads to a marked increase in the steady HERG current and kinetic changes that enhance repolarization forces; furthermore the Authors suggest that individuals with the T618I mutation may not be as resistant to class III antiarrhythmic drugs as the N588K mutation carriers.

The same mutation has recently been found in several members of four unrelated SQTs families.¹⁷ Hu and coworkers also describe in some of them two modifier gene variants that may affect the QT interval duration: the first, K897T, is believed to exert a modifying effect on the QT interval, but it is still controversial whether it increases or reduces I_{Kr} current.^{18,19} The second one, R1047L, has been shown to reduce I_{Kr} current.²⁰

Other genetic variants in *KCNH2* gene have been reported in the literature.^{21,22} It has been noted, however, that the finding of variants in any of the genes associated with SQTs is not sufficient to claim that they are the cause of the disease, unless they are absent in a relevant population of controls or functional analy-

ses are performed to confirm their pathogenetic role.²³ Figure 2 shows the localization of the described variants in HERG channel subunit.

In 2004 Bellocq *et al.*⁴ identified a mutation in the *KCNQ1* gene that codes I_{Ks} , the slow component of delayed rectifier channel current, in a 70-year-old patient with a QTc of 302 ms and aborted sudden death (valine to leucine at codon 307: V307L). The mutation caused a gain of function of I_{Ks} , resulting in a shortening of the action potential duration. A second mutation (valine to methionine at codon 141: V141M) in the S1 segment of *KCNQ1* was identified the following year by Hong *et al.*²⁴ in a baby girl born at 38 weeks, after labor induction prompted by bradycardia and irregular rhythm; her ECG revealed AF with slow ventricular response and short QT interval. The *KCNQ1* variant has been defined short QT syndrome type 2 (SQT2); loss-of-function mutations on the same gene are responsible for type 1 LQTS.

SQT3 was described by Priori *et al.*⁵ in 2005 and is associated with a gain of function mutation in the *KCNJ2* gene, encoding the inwardly rectifying channel protein Kir2.1. Two members of the same family had a change from aspartic acid to asparagine at position 172 (D172N). Functional analyses demonstrated a significant increase in the outward I_{K1} current. It is noteworthy that a reduced I_{K1} current is involved in the Andersen-Tawil syndrome (LQT7).

These mutations in *KCNH2*, *KCNQ1* and *KCNJ2* result in an increased activity (*gain of function* mutations) of outward potassium currents flowing during phases 2 and 3 of the car-

Figure 1. Unknown genotype. Male, 29 years old. A) Basal electrocardiogram (ECG): QT 300 ms, QTc 344 ms, QT/QTp 82%. B) ECG recorded following amiodarone: QT 400 ms, QTc 400 ms, QT/QTp 98%. Paper speed: 25 mm/s.

Table 1. Mutations in the potassium channel encoding-genes linked to short QT syndrome. For each subject QT/QTc interval, age at first clinical observation and clinical characteristics are reported.

	Family	Patient	Sex	Age at first clinical observation	QT	QTc	SD	aCA	Sync	AF	Other	Asymptomatic	Family history of SD
Gene: <i>KCNH2</i> Ref: 3 DNA: c.1764C > A AA change: p.N588K Region: S5-PORE loop (Extracellular)	EuroShort ¹	1	M	8 months	260	290	-	Yes	-	-	-	No	Yes
		2	F	31	250	290	-	-	-	-	Palpitations and VEBs	No	
		3	M	18	270	280	-	-	Yes	Yes	Palpitations and VEBs	No	
		4	F	Few days of life	210	309	-	-	-	-	-	Yes	
Gene: <i>KCNH2</i> Ref: 3 DNA: c.1764C > G AA change: p.N588K Region: S5-PORE loop (Extracellular)	EuroShort ¹	1	F	62	210	250	Yes	-	-	Yes	-	No	Yes
		2	M	8 months	260	300	-	Yes	Yes	-	-	No	
		3	F	51	270	295	-	-	-	Yes	-	No	
		4	F	40	240	268	-	-	-	Yes	-	No	
Gene: <i>KCNH2</i> Ref: 15 DNA: c.1764C > G AA change: p.N588K Region: S5-PORE loop (Extracellular)	3 ²	1	F	17	280	300	-	-	-	Yes	-	No	-
		2	F	51	260	289	-	-	-	Yes	-	No	
		3	M	24	272	267	-	-	-	Yes	-	No	
Gene: <i>KCNH2</i> Ref: 21 DNA: c.3404G > A AA change: p.R1135H Region: C-term (Cytoplasmic)	4 ²¹	1	M	34	-	329	-	-	-	-	Brugada pattern ECG	Yes	Yes
		2	M	30	-	377	-	-	-	-	-	Yes	
		3	F	-	-	379	-	-	-	-	-	Yes	
Gene: <i>KCNH2</i> Ref: 22 DNA: c.150G > T AA change: p.E50D Region: N-term (Cytoplasmic)	5 ²²	1	M	22	334	366	-	-	Yes	-	-	No	-
Gene: <i>KCNH2</i> Ref: 16 DNA: c.1853C > T AA change: p.T618I Region: pore helix (Intramembrane)	6 ¹⁶	1	M	45	-	298	-	-	-	-	Dizziness	No	Yes
		2	F	-	-	341	-	-	-	-	-	Yes	
		3	F	-	-	308	-	-	-	-	-	Yes	
		4	M	-	-	315	-	-	-	-	-	Yes	
Gene: <i>KCNH2</i> Ref: unpublished DNA: c.1853C > T AA change: p.T618I Region: pore helix (Intramembrane) + polymorphism rs1805121: T > C (p.L564L) <i>KCNH2</i> *	EuroShort (unpublished)	1	F	33	270	300	Yes	-	-	-	-	No	Yes
		2	M	14	260	273	-	-	-	-	-	Yes	
		3*	F	21	300	312	-	-	-	-	-	Yes	
Gene: <i>KCNH2</i> Ref: 17 DNA: c.1853C > T AA change: p.T618I Region: pore helix (Intramembrane) + polymorphism rs1805123: T > C (p.K897T) <i>KCNH2</i>	EuroShort ²⁷	1	F	46	280	340	-	-	-	-	Palpitations and VEBs	No	Yes
		2	M	15	277	320	-	-	-	-	-	Yes	
Gene: <i>KCNH2</i> Ref: 17 DNA: c.1853C > T AA change: p.T618I Region: pore helix (Intramembrane) + polymorphism rs36210421: C > A (p.R1047L) <i>KCNH2</i>	9 ¹⁷	1	F	-	270	300	-	-	-	-	-	No	Yes
		2	M	-	260	328	-	-	-	-	-	No	
		3	M	-	294	303	-	-	-	-	-	Yes	

SD, sudden death; aCA, aborted cardiac arrest; Sync, syncope; AF, atrial fibrillation; VEBs, ventricular ectopic beats. *KCNH2*: Ref Seq NM_000238.2, *KCNQ1*: RefSeq NM_000218.2, *KCNJ2*: RefSeq NM_000891.2.

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Table 1. Mutations in the potassium channel encoding-genes linked to short QT syndrome. For each subject QT/QTc interval, age at first clinical observation and clinical characteristics are reported.

	Family	Patient	Sex	Age at first clinical observation	QT	QTc	SD	aCA	Sync	AF	Other	Asymptomatic	Family history of SD
GENE: <i>KCNH2</i> Ref: 17 DNA: c.1853C > T AA change: p.T618I Region: pore helix (Intramembrane)	10 ¹⁷	1 2	F M	- -	240 -	243 -	- Yes	- -	- -	- -	- -	Yes No	Yes
GENE: <i>KCNQ1</i> Ref: 4 DNA: c.919G > C AA change: p.V307L pore helix (Intramembrane)	1 ⁴	1	M	70	290	302	-	Yes	-	-	-	No	-
GENE: <i>KCNQ1</i> Ref: 24 DNA: c.421G > A AA change: p.V141M (Transmembrane)	2 ²⁴	1	F	In utero	280	280	-	-	-	Yes	+	No	-
GENE: <i>KCNJ2</i> Ref: 5 DNA: c.514G > A AA change: p.D172N (Transmembrane)	1 ⁵	1 2	F M	- 15	- -	315 320	- -	- -	- Yes	- -	- Palpitations	Yes No	-

SD, sudden death; aCA, aborted cardiac arrest; Sync, syncope; AF, atrial fibrillation; VEBs, ventricular ectopic beats. *KCNH2*: Ref Seq NM_000238.2, *KCNQ1*: RefSeq NM_000218.2, *KCNJ2*: RefSeq NM_000891.2.

diac action potential, leading to the shortening of the plateau phase. Experimental studies have suggested that the abbreviation of action potential in SQTs is heterogeneous, hypothesizing the role of an increased transmural dispersion of repolarization in the genesis of the arrhythmias associated with short QT intervals.²⁵

Mutations in the three subunit comprising the L-type calcium channel have been shown to give rise to shorter than normal QT intervals (SQTs4-6, Table 2). In a study by Antzelevitch *et al.*¹⁰ 82 consecutive probands with a clinical diagnosis of Brugada syndrome were systematically screened for ion channel gene mutations. Seven index patients (8.5%) were found to have mutations in genes encoding the α 1- and β 2b- subunits of the cardiac L-type calcium channel responsible for a major loss of function. In three of these subjects a QTc $\leq$ 360 ms was detected. The first, a 25-year-old white male, presented with aborted SCD; his brother was also symptomatic, with syncope since age 21 years. Their QTc values were respectively 330 ms and 340 ms. Both carried a heterozygous c.1442C > T transition in exon 13 that predicted a substitution from serine to leucine at position 481 (S481L) of *CACNB2b* gene. The same mutation was found in four asymptomatic

members of the same family, in which the QTc values ranged from 340 ms to 370 ms. In the second proband, a 41-year-old male with AF and a QT interval of 300 ms (QTc 346 ms), a substitution of an adenine for a guanine at position 1468 in exon 10 of *CACNA1C*, which predicted substitution from glycine to arginine at position 490 (G490R), was found in association with two polymorphisms in the same gene. The G490R mutation was also found in

his two daughters, which displayed QTc values of 360 and 373 ms. In the latter, also a known polymorphism in *KCNH2*, K897T (18,19), was detected. The third proband was a 44-year-old male with QTc of 360 ms with a heterozygous c.116C > T transition in exon 2 of *CACNA1C*, which predicted a substitution of a valine for an alanine at position 39 (A39V).

In 2011 Templin *et al.*²⁶ reported the case of a 17-years-old female who had a sudden loss of

Figure 2. *KCNH2*-HERG channel subunit. Localization of the described mutations.

Table 2. Mutations in the calcium channel encoding-genes leading to a shortening of the QT interval. For each subject QT/QTc interval, age at first clinical observation and clinical characteristics are reported.

	Family	Patient	Sex	Age at first clinical observation	QT	QTc	SD	aCA	Sync	AF	Other	Asymptomatic	Family history of SD
GENE: <i>CACNB2b</i> (Isoform 2b) Ref: 10 DNA :c.1442C > T AA change: p.S481L	1 ¹⁰	1	M	25	-	330	-	Yes	-	-	Brugada pattern ECG	No	-
		2	M	21	-	340	-	-	Yes	-	Brugada pattern ECG	No	
		3	M	-	-	345	-	-	-	-	Brugada pattern ECG	Yes	
		4	F	-	-	370	-	-	-	-	Brugada pattern ECG	Yes	
		5	F	-	-	368	-	-	-	-	Brugada pattern ECG	Yes	
		6	F	-	-	340	-	-	-	-	Brugada pattern ECG	Yes	
GENE: <i>CACNA1C</i> Ref: 10 DNA:c.1468G>A AA change: p.G490R (Cytoplasmic, loop between domains I and II) + polymorphism rs10848683: C > T, rs10774053: A > G (p. P1820L/V1821M) <i>CACNA1C</i> + polymorphism rs1805123: T > C (p. K897T) <i>KCNH2</i> ^{**}	2 ¹⁰	1*	M	41	300	346	-	-	-	Yes	Brugada pattern ECG	No	Yes
		2	F	-	-	360	-	-	-	-	-	Yes	
		3**	F	-	-	373	-	-	-	-	-	Yes	
GENE: <i>CACNA1C</i> Ref: 10 DNA: c.116C > T AA change: p.A39V N-term (Cytoplasmic)	3 ¹⁰	1	M	44	-	360	-	-	-	-	Brugada pattern ECG	Yes	Yes
GENE: <i>CACNA2D1</i> Ref: 26 DNA: c.2264G > C AA change: p.S775T (External carboxyl terminal)	4 ²⁶	1	F	17	317	329	-	Yes	-	-	-	No	-
		2	M	-	-	362	-	-	-	-	-	Yes	
		3	F	-	-	432	-	-	-	-	-	Yes	

SD, sudden death; aCA, aborted cardiac arrest; Sync, syncope; AF, atrial fibrillation.

consciousness. Basic life support was administered immediately and the initial rhythm recorded was ventricular fibrillation (VF), which was successfully defibrillated. The ECG showed a short QT interval and tall, symmetrical T waves, with intermittent incomplete right bundle branch block. Flecainide provocation did not reveal a typical Brugada ECG pattern, but some non-specific repolarization changes in lead V1. A novel heterozygous mutation in *CACNA2D1* gene predicting a substitution of a threonine for serine at residue 755 (S755T) of $\text{Ca}_v\alpha_2\delta$ -1 subunit of the cardiac L type calcium channel was found. Functional analyses revealed that this variant reduces the $\text{Ca}_v\alpha_1$ -mediated current, but the molecular mechanisms underlying these effects are only poorly understood. Two other members of the family, the father and the paternal grandmother of the young woman, carried the same mutation, and their ECG showed QTc intervals of 362 ms and 432 ms respectively. They were totally asymptomatic and no prior SD event or arrhythmia had occurred in this family before.

Mutations in the L-type calcium channel (LTCC) have been detected in a high percentage of probands with J-wave syndromes,

Brugada syndrome and Early repolarization syndrome.¹⁸

The *KCNH2* mutations (SQTS1) are the most frequently reported in the literature, while *KCNQ1* and *KCNJ2* are only sporadic. Today, in our experience, a mutation in the *KCNH2*-HERG gene is found in 36% of the analyzed patients (18/50), while a mutation in the LTCC encoding genes is present in 6% of them (unpublished data from the EuroShort Registry).

Clinical findings

The clinical presentation of SQTS is quite variable. Initial presentation and clinical course differ among families and members of the same family, ranging from asymptomatic carriers, to patients with AF, to those suffering VF or SD (Tables 1 and 2). This reflects the incomplete penetrance and the variable expression of genetic mutations underlying the disease, and could depend also on the presence of additional genetic variants or environmental factors. Data from the Euroshort

Registry²⁷ show a prevalence of affected males (75%), with a mean age at observation of 28 ± 17 years. A family history of SD is present in 50% of index patients and 62% of the whole population reported symptoms. Cardiac arrest represents the first clinical presentation in more than one third of the cases. Most of the events occurred between the second and the fourth decade, mainly in males; however, it was observed also in infants in their first months of life, suggesting that SQTS may be a cause of sudden infant death syndrome. Events have occurred both at rest and during exertion or emotion; no specific trigger has been associated up to now to mutations in different genes. Syncope is the first symptom in about 15% of patients, and it is probably due to self-terminating episodes of VT or VF. Palpitations, often with evidence of AF, represent another common clinical presentation. AF has been observed in individuals of all ages, also under 35 years and is probably related to the short atrial refractory periods. In about 40% of the subjects no symptoms were detected, and the diagnosis was made due to a family history of short QT syndrome.

Information about genotype-phenotype cor-

relation in SQTS are largely speculative thus far, due to the limited available data. Based on our experience, we can state that patients with N588K or T618I mutation in *KCNH2* gene show specific characteristics, such as a greater proportion of affected females and a higher prevalence of AF (N588K-*KCNH2* mutation). Moreover, they exhibit shorter QT intervals and effective refractory periods (ERPs) at baseline and a greater response to antiarrhythmic treatment with hydroquinidine (HQ).

Diagnosis

Diagnosis of SQTS is based on the finding of a constantly short QT interval at ECG. Of course, acquired causes of short QT interval such as sinus tachycardia, hyperthermia, electrolyte abnormalities, acidosis, increased vagal tone, and digitalis toxicity²⁸ must be carefully ruled out. Structural heart disease is generally absent, as demonstrated by echocardiography, magnetic resonance and in some cases by autopsy.

Holter recording and stress test document a regular behaviour of the heart rate during activity, but only a small variation of the QT interval in relation to the RR cycle. In SQTS patients the QT interval does not show the physiological shortening in response to an increasing heart rate, but decreases only slightly, due to the enhanced repolarizing currents.^{1,9} Wolpert *et al.*²⁹ demonstrated that this lack of adaptation of the QT interval results in a less steep slope of the QT-RR relationship in patients with SQTS1 as compared to control subjects. Thus, the analysis of the QT behaviour during 24-hour ECG recordings and stress test represents a very helpful element in the diagnosis of SQTS.

Electrophysiological study (EPS) has a role in confirming the diagnosis, showing short ventricular refractory periods (range 140-200 ms at a cycle length between 500 and 600 ms), but its role in risk stratification is not clear. At programmed ventricular stimulation VF is induced in about 60% of cases, frequently by mechanical contact during catheter positioning, but EPS sensitivity in predicting spontaneous events is very low.²⁷ Also atrial ERPs are very short and sustained AF is frequently induced during programmed atrial stimulation.

Management

Given the high incidence of SD, an implantable cardioverter-defibrillator (ICD) represents the treatment of choice in high-risk individuals, including those with aborted cardiac arrest or syncope. ICD has also been pro-

posed to asymptomatic subjects with a strong family history of SD, even without induced ventricular arrhythmias.⁹

However, the implant of an ICD is not accepted or not feasible in all patients, for example in children, because of technical difficulties and a high rate of complications.²⁷

A common complication in the first SQTS patients who received an ICD was the occurrence of inappropriate shocks, due to oversensing of the T wave.^{30,31} The tall, peaked, and closely coupled T waves were mistakenly sensed as R waves, leading to double counting and inappropriate ICD discharges. Adequate reprogramming of the decay delay, sensitivity, or both helped preventing this problem.

Investigators have tried a variety of antiarrhythmic agents in an attempt to correct the electrophysiological anomalies recognized in SQTS patients. Even before the identification of the gain-of function mutation in *KCNH2* in the first described families, the very short QT interval and the symmetric T waves of high amplitude led to the hypothesis of an increased phase 2 or phase 3 potassium currents; for this reason selective I_{Kr} blocking agents were tested (sotalol and ibutilide).³² These drugs failed to produce an increase in the QT interval in patients with SQTS1, and subsequent genetic studies showed that the N588K mutation in *KCNH2* reduced the sensitivity of the channel to sotalol.³ Among the other drugs, flecainide caused only a slight QT prolongation (mainly due to an increase in the QRS duration) in the 4 patients who tried it. The normalization of

the QT interval was instead obtained with HQ, which also proved to be effective in lengthening ventricular refractory periods and made VF non-inducible.³² Wolpert and colleagues later demonstrated that the N588K-*KCNH2* mutation produced a 5.8-fold decrease in the I_{Kr} channel-blocking effect of HQ, in contrast to the 20-fold decrease in the effect of sotalol.²⁹ The long-term efficacy of HQ in SQTS has been recently confirmed by our group.²⁷ Twelve patients had been receiving HQ for a mean period of 76 ± 30 months; HQ induced normalization of the QT interval and of the ERPs in patients with *KCNH2* mutations, both N588K and T618I carriers (Figure 3). In patients with different or unknown genotype, a lower and less homogeneous QTc increment was observed. However, HQ prevented both induction of VF at EPS and arrhythmic events at follow-up in all subjects. HQ has been used in adults mainly as a prophylaxis for AF or flutter, but also in patients who had declined an ICD implant and in children both as primary and secondary prevention after VF. HQ served as a valuable bridge to ICD.

Recently, *in vitro* studies by Sun *et al.*¹⁶ demonstrated that the T618I-*KCNH2* mutation is associated with a smaller loss of the inhibitory effect of sotalol on I_{Kr} channel, due to a less profound effect on inactivation of HERG current. For this reason the authors suggest that the T618I mutation carriers might be treated with sotalol; however, clinical confirmation is lacking.

Other antiarrhythmic drugs that have been

Figure 3. p.T618I-*KCNH2* (SQTS1). Male, 15 years old. A) Basal electrocardiogram (ECG): QT 250 ms, QTc 337 ms, QT/QTp 80%. B) ECG recorded following hydroquinidine: QT 320 ms, QTc 406 ms, QT/QTp 96%. Paper speed: 25 mm/s.

tested clinically include propafenone, which prevented AF but did not prolong the QT interval,¹⁵ and amiodarone, which was successfully used to prevent polymorphic ventricular tachycardia recurrences in two patients with SQTs and unknown genotype (Figure 1).^{27,33} Dysopyramide has been shown to reduce I_{Kr} current blockade only slightly (1.5 fold) in patch-clamp studies on cells expressing the N588K-*KCNH2* mutation;³⁴ however in the clinical setting the data are limited.^{35,36}

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